Institut Pasteur

28, RUE DU Dr ROUX, 75724 PARIS CEDEX 15

TELEX PASTEUR 250609 F

TEL. (1) 306.19.19

Paris, May 14th, 1985.

Dr. Harold VARMUS
UNIVERSITY OF CALIFORNIA
SCHOOL OF MEDICINE
Department of Microbiology
San Francisco
Californie 94142
U. S. A.

Dear Harold,

Thank you for inviting me to join the subcommittee for nomenclature on human retroviruses. Here are my proposals for the name of the retrovirus involved in AIDS and related disease.

1. On the basis of available data, I should like to demonstrate that the human AIDS agent (LAV) is a new retrovirus species not closely related to HTLV1 and 2 :

   1°/ Proteins : the gag and pol proteins are the most conserved structural elements among retroviruses. Common antigenic determinants are found in the major gag proteins of many mammalian retroviruses (rodent, Primate). In contrast, the p25 of LAV does not react with antibodies against rodent or Primate core proteins. Homologous radioimmunocompetition assay have shown no cross-reactivity between p24 of HTLV-I and -II in one hand, and LAV (HTLV-III) p25. The homologous regions found in the protease, the polymerase domains are found in many animal retroviruses, including RSV (1) and MoMuLV.
   Actually, the endonuclease protein sequence is phylogenetically distant to all other retroviral endonuclease sequences (Fig. 2 Réf. 2). Also the reverse transcriptase protein sequence is more phylogenetically distant to that of HTLV than RSV is to HTLV-I.
   A computerized search for aminoacid sequence homology for the other genes (Q, F and env) have failed to find significant homology with X and env genes of HTLV-I and -II. We have asked others to independently execute the same searches using different programs and algorithms. They too do not find significant homology. Therefore, the previously membrane immunofluorescence data reported by Essex et coll. on cross-reactivity between HTLV-I and LAV env proteins must find other explanation (carbohydrate, cellular antigens, configuration).

   (1) S. Broome and W. Gilbert, Cell 40, 1985, 537-546
   (2) S. Wain-Hobson, M. Alizon and L. Montagnier, Nature 313, 1985, 743.

./.

2°/ Nucleic acids :

1) The absence of molecular hybridization between HTLV-I, -II and LAV has been confirmed by five independent laboratories.

2) No significant nucleotide sequence homology between HTLV-I and LAV, except for 16 bases in the beginning of the pol region (protease domain) of LAV.

3) A longer genome (9,2 Kb wrt 8,5 Kb for HTLV-I).

4) A relatively A/T rich genome (58%) as opposed to 47% for HTLV-I.

5) A reduced CpG frequency (0.9%) as opposed to 3.9%.

6) A very differently organized genome in which pol and env do not overlap (unprecedented). An open reading frame (Q) of 192 aas overlaps the end of pol and is followed by an apparently intragenic region. An open reading frame (F) of 206 aas follows directly env and is half encoded by the LTR. Both F and Q are transcribed and therefore most probably encode protein.

7) Orf env is unusually long ($\simeq$ 860 aas).

8) A differently organized protease domain. For LAV, it is part of a pol polyprotein, for HTLV-I/BLV, it is not.

9) Relatively short ($<$ 100 bp) U5 and R elements.

10) A polyadenylation signal sequence (AATAAA) within R.

11) A $tRNA_3^{lys}$(-) strand primer as opposed to $tRNA^{pro}$ used by most mammalian retroviruses.

12) A purine tract that resembles, if anything, that of MMTV.

13) No long direct repeats in the LTR.

14) A possible discontinuous (+) strand DNA synthesis as reported for visna.

These features in common are shared by many retroviruses :

a) Trans-activation has been shown for HTLV-I, LAV, BLV and RSV.

b) Mg^{2+} preferance of the reverse transcriptase is very frequent (Lentiviruses, MMTV, RSV, HTLV/BLV), Mn^{2+} being found only for the Spumaviruses and the MoMuLV related viruses (SSV, FeLV, etc ...).

c) Double -or triple- spliced mRNAs. These are clearly the case for LAV and HTLV-I. Do we really know the detailed splicing patterns for MPMV and visna for example ?

3°/ Morphology : EM studies show a different structure of LAV, close to that of EIAV and different from that HTLV-I, which is similar to that of C-type murine retroviruses. Three morphological aspects of the virus can be seen in sections of infected lymphocytes or certain lymphoid cell lines :

* Budding particles at the cell surface : the ribonucleoprotein core forms a dense crescent which is linked to the plasma membrane by

./.

structured material. This aspect differs from that in C-type particle or Human T Leukemia virus type I, in which the core in formation is separated from the plasma membrane by an electron lucent space. It differs also from the budding D-type particles in which the core is already condensed during morphogenesis.

* Immature free particles : this is an intermediate stage in which the release particles still exhibits an uncondensed core. Transition stages of condensation can be observed.

* Mature virions show a small eccentric core, sometimes bar-shaped.

4°/ Biology :

a) *In vitro* tropism for T4 :

This is the unique apparent similarity between HTLVs and LAV. However, it should be noted that, unlike the situation for LAV, the tropism of HTLV for T4 cells has not been directly demonstrated by infecting purified T4 and T8 cells with free virus. While most of the lines derived from leukemic patients or *in vitro* transformed by HTLV-I harbor the T4 phenotype, the phenotype of the original target cells is not known. In addition, the molecular basis of LAV tropism for $T4^+$ cells is known : the T4 glycoprotein serves (at least in part) as receptor for the virus. This is not the case of HTLV-I and -II, in which the tropism seems to depend on genomic regulatory elements. Moreover, many human viruses (adeno, hepatitis, papova) and animal retroviruses (leukemogenic) exhibit tropism for T and B cells. Accurate separation between subsets of T cells have not yet been performed in these cases, so that T4 tropism may not be a unique feature of the human retroviruses LAV and HTLV. Finally, it is distinctly possible that LAV may not be strictly T-lymphotropic since the finding of viral replication -as judged by in situ hybridization- in the glial cells of the brain suggests a certain neurotropism as well.

b) *In vitro* cytopathogenicity :

LAV belongs to the cytopathic retroviruses (REV, visna, EIAV, ...). There is no reported instance of transformation by the virus leading to immortalized lines or even stimulation of cell growth. This is in contrast with HTLV-I and -II, whose infection (generally by cocultivation) gives rise to permanently activated lymphoblastic T cell lines.

c) *In vivo* pathogenicity :

There exists abundant indirect evidence that LAV is the causative agent of irreversible, profound, T4 cell-mediated immune deficiency. It is not known whether the lethal disease is linked directly to cytopathic effect of the virus or of viral protein on the $T4^+$ cells, or is due to indirect mechanisms, co-factors and host responses. Recently, transfusion cases have shown that acute LAV infection results in the signs described as lymphadenopathy syndrome and AIDS related complex.

./.

The situation of irreversible immune deficiency may result in the appearance of cancers (B lymphomas, disseminated and aggressive form of Kaposi sarcoma), but the virus has not been shown to cause directly these cancers or any other cancers or leukemias. Sero-epidemiological data indicate a causal association between HTLV-I infection and adult T cell leukemia or lymphoma.
Many other lymphotropic viruses can cause a more or less severe immune depression. However, the profound and irreversible character of T4 immune deficiency induced by LAV is striking and so far unique.
In summary, LAV (or its other names HTLV-III or ARV) clearly differs from HTLV-I and -II on the following criteria :

. ultrastructure
. genome structure
. lack of homology in primary sequence of DNA and aminoacids
. lack of relevant cross-antigenicity of proteins
. size of envelope protein
. pathogenicity *in vitro* and *in vivo*.

Therefore, it is the prototype of a new human retrovirus species and deserves a name which clearly distinguishes it from, and avoids confusion with, the HTLVs.

5°/ Analogy with Lentiviruses

Finally, the striking homologies with visna virus should caution the inclusion of the AIDS agent into the oncovirus subfamily of retroviruses. Rather it is distinctly possible that LAV could be the prototype human lentivirus.
The similarities are :

. Persistant infection in the presence of circulating antibody *in vivo*
. Cytopathic effect *in vitro*
. Morphology
. A 9,2 Kb genome
. A virtually identical base composition

	LAV	VISNA
U	22.2 %	22 %
C	17.8 %	16 %
A	35.8 %	36 %
G	24.2 %	26 %

. A Mg^{2+} preference for the reverse transcriptase
. A comparably sized gag precursor 55 Kd (cleared to three)
. Very large envelope glycoproteins (110 Kd-LAV ; 135 Kd-visna).

We have reported a common epitope between the major core proteins of LAV and EIAV.

./.

2. Existing names :

Initial names of the AIDS virus : our approach in studying the AIDS retrovirus and its relationship with known retroviruses, such as HTLV-I and -II, has been always to take into account scientific facts without preconcieved ideas : at the beginning, it was not clear how different from the HTLVs the new virus we had isolated was and, without definite evidence that it was the causative agent of AIDS, we defined it by its main property known at that time : T lymphotropism.
The name HTLV had at that time a very accurate and different meaning, that of Human T-cell Leukemia Virus : this definition was internationally recognized and was the subject of a letter to Science (222, 1178, 1983) signed by three Japanese scientists, Drs. Watanabe, Seiki and Yoshida, with the agreement of 12 other scientists, including Dr. Gallo and Dr. Weiss. In a review article published in 1982 on HTLV, Dr. Gallo and Dr. Reitz clearly stated that HTLV-II was a subtype of HTLV and that each strain should be given a roman numeral (Journal of National Cancer Institute 62, 1211, 1982).
We never considered -subsequent data has proved us right- that our isolate was a strain of HTLV, and accordingly we never called it HTLV-III. Indeed, we were able to show that our virus was not morphologically and immunologically related to HTLV-I and -II and when we had several isolates from LAS and AIDS patients, we called these isolates, respectively Lymphadenopathy Associated Virus (LAV) and Immune Deficiency Associated Viruses (IDAV). Although we could not distinguish these various isolates, the possibility remained -and still remains- that subtle genetic changes may explain these different pathogenicities. Those terms have been used in public presentations and publications of our data before those of Gallo on HTLV-III :
Ref. = D. Klatzmann et al., International Congress on Immunology, Kyoto, August 1983 ; L. Montagnier et al., in Cold Spring Harbor meeting on Human T Leukemia/Lymphoma Viruses, September 1983 ; F. Barré-Sinoussi et al., in Manipulation of host defence mechanisms, Nigata, Japan, November 1983 ; D. Klatzmann et al., AIDS Conference on the New York Academy of Science, November 1983 ; J.C. Chermann et al., UCLA Symposium on AIDS, Park City, February 1984 ; L. Montagnier et al., Ann. of Virol., March 1984 ; E. Vilmer et al., Lancet, April 7 1984).

3. Proposed name :

Since the term LAV has been more widely used by various laboratories than IDAV, we have kept using the former for the sake of simplicity. We never used the term HTLV for meaning T-cell lymphotropic virus, and we think that such use is a source of confusion, since all groups working on the AIDS virus agree now that this virus is not close to HTLV-I and -II (see above). As for most viruses, I think the most suitable definition for this virus is by its pathogenicity. I propose the name of Lymphadenopathy-AIDS virus, since we have now good evidence that it causes more frequently generalized lymphadenopathy and more rarely AIDS. This name will not be frigtening for infected people since lymphadenopathy is a benigh disease.

./.

The initial H for human is not always used for human viruses : for example Hepatits, Herpes viruses, polio, etc ... Therefore, it is not a necessity in the case of the AIDS virus.

Sincerely yours,

L Montagnier

Luc Montagnier, M.D.
Head of Virology Department